REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested. Claims 1-14, 16 and 18-22 are pending in the present application.

In the Office Action, the Examiner rejected claims 1-3, 9-14, 16 and 18-22 under 35 U.S.C. § 102(b) as being anticipated by Sherman et al., United States Patent No. 6,274,171 (hereinafter "the Sherman reference") and rejected claims 1-14, 16 and 18-22 under 35 U.S.C. § 103(a) as being unpatentable over the Sherman reference in view of Jerussi et al., United States Patent No. 6,342,533 (hereinafter "the Jerussi reference").

In an effort to expedite prosecution of the present application, Applicants have amended claim 1, the only pending independent claim to specifically indicate that both the immediate release pellet and the extended release pellet comprise an inert **sugar** pellet. No new matter is added by this amendment. Support can be found in claim 6 as originally filed, on page 6, lines 5-15 of the present specification and Examples 1, 2 and 3 that appear on pages 10-17 of the present specification.

Applicants respectfully submit that the presently amended claims are patentable over the Sherman reference either alone or combined with the Jerussi reference.

The Examiner is correct that the Sherman reference discloses an extended release, i.e. controlled release, venlafaxine formulation that comprises coated

venlafaxine pellets or spheroids. The coated venlafaxine pellets disclosed in the Sherman reference are prepared by an extrusion/spheronization process and are prepared with microcrystalline cellulose. There is no disclosure or suggestion in the Sherman reference that sugar could be used to prepare the venlafaxine pellets as required by the amended claims in the present application.

Microcrystalline cellulose is a water insoluble material. Sugar is a water soluble material. Attached hereto as Exhibit A are portions from the Handbook of Pharmaceutical Excipients, 4th ed. that confirms the different solubilities. In view of the differences in solubility, an individual of ordinary skill would not be lead to substitute sugar for the microcrystalline cellulose of the Sherman reference, especially in venlafaxine pellets coated with a water insoluble polymer as required by the pending claims. The differences in solubility would produce different osmotic pressures that could adversely affect that the controlled release of venlafaxine from the coated pellets.

In view of this difference between the pending claims and the teachings of the Sherman reference, it is respectfully submitted that the pending claims are patentable over the teachings of the Sherman reference.

The addition of the Jerussi reference fails to overcome, the deficiencies of the Sherman reference. The Jerussi reference fails to provide any guidance for preparing a controlled release formulation as recited in the pending claims. The Jerussi reference provides a very general disclosure on preparing venlafaxine formulations. See Col. 16, line 31 to Col. 20, line 27. No where in this general

disclosure is there any suggestion to prepare a controlled release venlafaxine formulation as recited in the pending claims which comprises both an immediate release venlafaxine pellet and an extended release venlafaxine pellet wherein both pellets contain sugar.

The Jerussi reference does disclose a capsule and a tablet venlafaxine formulation. Col. 27, line 49 to Col. 28, line 35. Neither of these formulations employ sugar. Moreover, neither of these formulations employs a combination of an immediate release venlafaxine pellet and an extended release venlafaxine pellet. Based upon the use the disintegrant, croscarmellose, in both formulations disclosed in the Jerussi reference, it is believed that both formulations are immediate release formulations and not controlled release formulations as required by the pending claims.

It is further submitted that the addition of the Jerussi reference to the Sherman reference teaches away from the present invention. Specifically, the Jerussi reference teaches that mono and disaccharides can cause isomers of venlafaxine to decompose and therefore the use of mono and disaccharides in formulations should be avoided. See Col. 18, lines 26-32. In light of teaching and the overwhelming disclosures in the Sherman and Jerussi references to use microcrystalline cellulose, it is respectfully submitted that an individual of ordinary skill would not be motivated to use sugar, a disaccharide, to prepare an immediate release venlafaxine pellet and an extended release venlafaxine pellet as required by the pending claims.

Based upon the foregoing amendments and representations, Applicants respectfully submit that the rejection of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

Martin P. Endres
Reg. No. 35,498

MAILING ADDRESS:
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2601
(212) 302-8989

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450 on Nov. 9, 2007

Martin Endres

Handbook of Pharmaceutical Excipients

FOURTH EDITION

Edited by

Raymond C Rowe

BPharm, PhD, DSc, FRPharmS, CChem, FRSC, CPhys, MInstP

Senior Principal Scientist

AstraZeneca

Macclesfield, UK

Paul J Sheskey

BSc, RPh

Technical Service Leader

Water Soluble Polymers R&D

The Dow Chemical Company

Midland

MI, USA

Paul J Weller

BSc, MSc, CChem, MRSC

Publisher – Science and Practice

Royal Pharmaceutical Society of Great Britain

London, UK

London • Chicago

Pharmaceutical Press

APhA

American Pharmaceutical Association

Published by the Pharmaceutical Press
Publications division of the Royal Pharmaceutical Society of Great Britain

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 206, Grayslake, IL 60030-7820, USA

and the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA

First edition published 1986
Second edition published 1994
Third edition published 2000
Fourth edition published 2003

Text design by Barker Hilsdon, Lyme Regis
Typeset by Bibliocraft Ltd, Dundee
Printed in Great Britain by The Bath Press, Bath

ISBN 0 85369 472 9 (UK)
ISBN 1 58212 022 6 (USA)

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
Handbook of pharmaceutical excipients.– 4th ed. / edited by Raymond C. Rowe, Paul J. Sheskey, Paul J. Weller.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-58212-022-6 (alk. paper) – ISBN 0-85369-472-9 (alk. paper)
1. Excipients–Handbooks, manuals, etc.
[DNLM: 1. Excipients–Handbooks. QV 735 H236 2003] I. Rowe, Raymond C. II. Sheskey, Paul J. III. Weller, Paul J.

RS201.E87H36 2003
615'.19–dc21

2003002641

Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose

2 Synonyms

Avicel PH; *Celex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; E460; *Emcocel*; *Ethispheres*; *Fibrocel*; *Pharmacel*; *Tabulose*; *Vivapur*.

3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

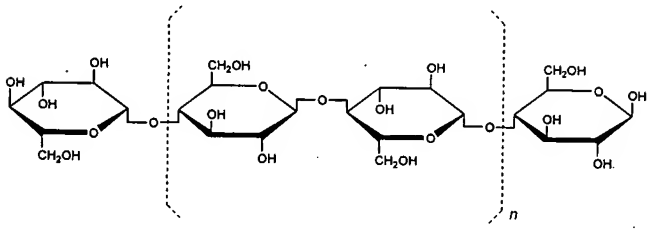
4 Empirical Formula

$(C_6H_{10}O_5)_n$
where $n \approx 220$.

Molecular Weight

≈36 000

5 Structural Formula



6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products; *see* Table I.

8 Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2002 Suppl 4.2	USPNF 20
Identification	+	+	+
Characters	+	+	—
pH	5.0–7.0	5.0–7.5	5.0–7.0
Bulk density	+	—	+
Loss on drying	⩽7.0%	⩽6.0%	⩽7.0%
Residue on ignition	⩽0.05%	—	⩽0.05%
Conductivity	+	—	+
Sulfated ash	—	⩽0.1%	—
Ether-soluble substances	⩽0.05%	⩽0.05%	⩽0.05%
Water-soluble substances	+	⩽0.25%	⩽0.24%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Starch	—	+	—
Organic volatile impurities	—	—	+
Microbial limits	+	+	+

10 Typical Properties

Angle of repose:
49° for *Ceolus KG*
34.4° for *Emcocel 90M*[9]

Density (bulk):
0.337 g/cm^3
0.32 g/cm^3 for *Avicel PH-101*[10]
0.29 g/cm^3 for *Emcocel 90M*[9]

Density (tapped):
0.478 g/cm^3
0.45 g/cm^3 for *Avicel PH-101*[10]
0.35 g/cm^3 for *Emcocel 90M*[9]

Density (true): 1.512–1.668 g/cm^3

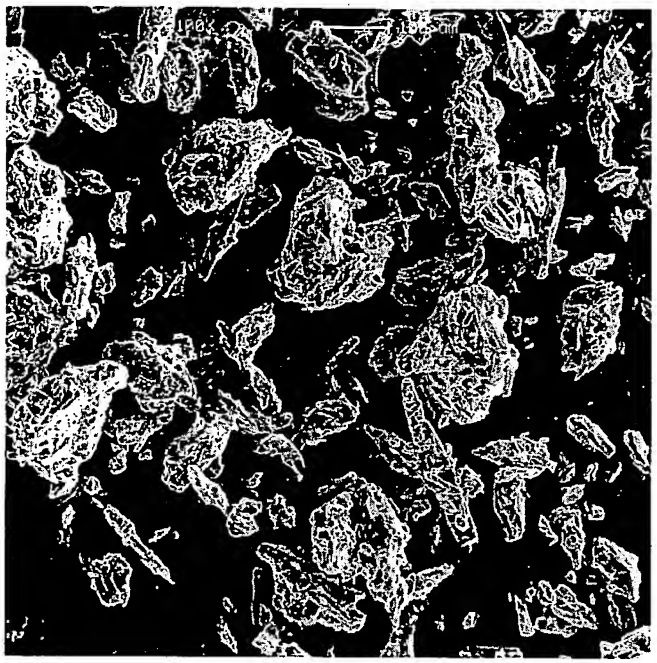
Flowability: 1.41 g/s for *Emcocel 90M*.[9]

Melting point: chars at 260–270°C.

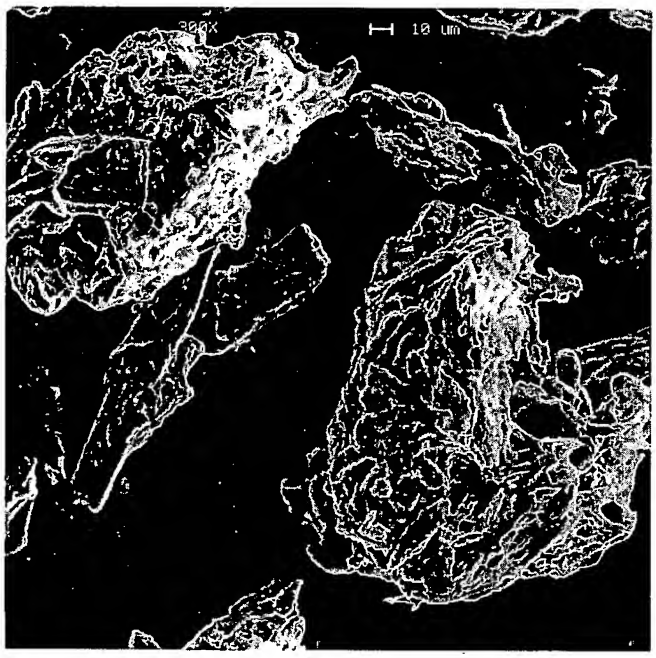
Moisture content: typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.[11] *See* Table III.

Particle size distribution: typical mean particle size is 20–200 μm. Different grades may have a different nominal mean particle size; *see* Table III.

SEM: 1
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals Co.
Lot No.: 98662
Magnification: 100 ×



SEM: 2
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals Co.
Lot No.: 98662
Magnification: 300 ×



Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area:
1.06–1.12 m^2/g for *Avicel PH-101*
1.21–1.30 m^2/g for *Avicel PH-102*
0.78–1.18 m^2/g for *Avicel PH-200*

11 Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

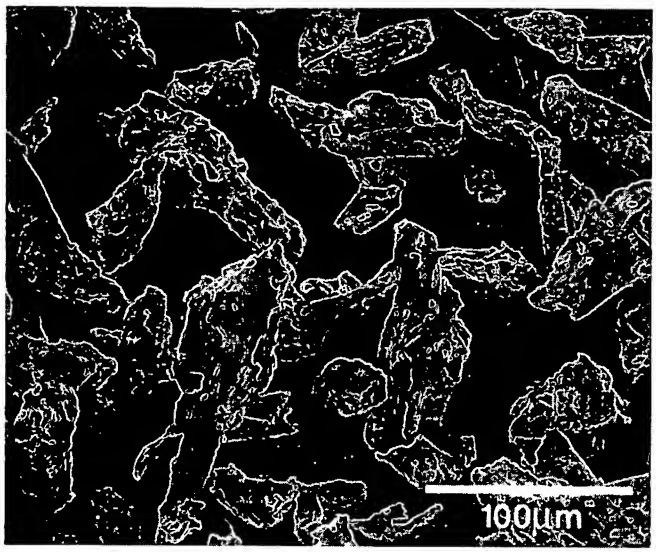
Microcrystalline cellulose is incompatible with strong oxidizing agents.

Table III: Properties of selected commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101[a]	50	60	≤1.0	≤5.0
		200	≤30.0	
Avicel PH-102[a]	100	60	≤8.0	≤5.0
		200	≥45.0	
Avicel PH-103[a]	50	60	≤1.0	≤3.0
		200	≤30.0	
Avicel PH-105[a]	20	400	≤1.0	≤5.0
Avicel PH-112[a]	100	60	≤8.0	≤1.5
Avicel PH-113[a]	50	60	≤1.0	≤1.5
		200	≤30.0	
Avicel PH-200[a]	180	60	≥10.0	≤5.0
		100	≥50.0	
Avicel PH-301[a]	50	60	≤1.0	≤5.0
		200	≤30.0	
Avicel PH-302[a]	100	60	≤8.0	≤5.0
		200	≥45.0	
Celex 101[b]	75	60	≤1.0	≤5.0
		200	≥30.0	
Ceolus KG-802[c]	50	60	≤0.5	≤6.0
		200	≤30.0	
Emcocel 50M[d]	51	60	≤0.25	≤5.0
		200	≤30.0	
Emcocel 90M[d]	91	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 101[e]	50	60	≤1.0	≤5.0
		200	≤30.0	
Vivapur 102[e]	90	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 12[e]	160	38	≤1.0	≤5.0
		94	≤50.0	

Suppliers: [a]FMC Biopolymer; [b]International Specialty Products; [c]Asahi Kasei Corporation; [d]Penwest Pharmaceuticals Co.; [e]J Rettenmaier & Söhne GmbH.

SEM: 3
Excipient: Microcrystalline cellulose
Manufacturer: FMC Biopolymer
Magnification: 100 ×



13 Method of Manufacture

Microcrystalline cellulose is manufactured by the controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14 Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.[13]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxymethylcellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose; silicified microcrystalline cellulose.

Microcrystalline cellulose and carrageenan

Synonyms: *Lustre Clear.*
Comments: *Lustre Clear* (FMC Biopolymer) is an aqueous film coating combining microcrystalline cellulose and carrageenan.

Microcrystalline cellulose and carboxymethylcellulose sodium

Synonyms: *Avicel CL-611*; *Avicel RC-581*; *Avicel RC-591*; colloidal cellulose; dispersible cellulose.
Appearance: white, odorless and tasteless, hygroscopic powder.
Acidity/alkalinity: pH = 6–8 for a 1.2% w/v aqueous dispersion.
Moisture content: not more than 6.0% w/w.
Particle size distribution:
Avicel CL-611: ⩽0.1% retained on a #60 mesh and ⩽50% retained on a #325 mesh
Avicel RC-581: ⩽0.1% retained on a #60 mesh and ⩽35% retained on a #200 mesh
Avicel RC-591: ⩽0.1% retained on a #60 mesh and ⩽45% retained on a #325 mesh
Solubility: practically insoluble in dilute acids and organic solvents. Partially soluble in dilute alkali and water (carboxymethylcellulose sodium fraction).
Viscosity (dynamic):
5–20 mPa s (5–20 cP) for a 1.2% w/v aqueous dispersion of *Avicel CL-611*
72–168 mPa s (72–168 cP) for *Avicel RC-581* at the same concentration
39–91 mPa s (39–91 cP) for *Avicel RC-591* at the same concentration
Comments: mixtures of microcrystalline cellulose and carboxymethylcellulose sodium that are dispersible in water and produce thixotropic gels are suitable as suspending vehicles in pharmaceutical formulations. The amount of carboxymethylcellulose present can vary between 8.3% and 18.8% w/w depending upon the grade of material.

Microcrystalline cellulose and guar gum

Synonyms: *Avicel CE-15.*
Comments: *Avicel CE-15* (FMC Biopolymer) is a coprocessed mixture of microcrystalline cellulose and guar gum used in chewable tablet formulations.

18 Comments

Several different grades of microcrystalline cellulose are commercially available that differ in their method of manufacture,[14,15] particle size, moisture, flow, and other physical properties.[16–25] The larger-particle-size grades generally provide better flow properties in pharmaceutical machinery. Low-moisture grades are used with moisture-sensitive materials. Higher-density grades have improved flowability.

Several coprocessed mixtures of microcrystalline cellulose with other excipients such as carrageenan, carboxymethylcellulose sodium, and guar gum are commercially available; *see* Section 17.

Celphere (Asahi Kasei Corporation) is a pure spheronized microcrystalline cellulose available in several different particle size ranges.

19 Specific References

1 Enézian GM. Direct compression of tablets using microcrystalline cellulose [in French]. *Pharm Acta Helv* 1972; 47: 321–363.
2 Lerk CF, Bolhuis GK. Comparative evaluation of excipients for direct compression I. *Pharm Weekbl* 1973; 108: 469–481.
3 Lerk CF, Bolhuis GK, de Boer AH. Comparative evaluation of excipients for direct compression II. *Pharm Weekbl* 1974; 109: 945–955.
4 Lamberson RF, Raynor GE. Tableting properties of microcrystalline cellulose. *Manuf Chem Aerosol News* 1976; 47(6): 55–61.
5 Lerk CF, Bolhuis GK, de Boer AH. Effect of microcrystalline cellulose on liquid penetration in and disintegration of directly compressed tablets. *J Pharm Sci* 1979; 68: 205–211.
6 Chilamkurti RN, Rhodes CT, Schwartz JB. Some studies on compression properties of tablet matrices using a computerized instrumented press. *Drug Dev Ind Pharm* 1982; 8: 63–86.
7 Wallace JW, Capozzi JT, Shangraw RF. Performance of pharmaceutical filler/binders as related to methods of powder characterization. *Pharm Technol* 1983; 7(9): 94–104.
8 Omray A, Omray P. Evaluation of microcrystalline cellulose as a glidant. *Indian J Pharm Sci* 1986; 48: 20–22.
9 Celik M, Okutgen E. A feasibility study for the development of a prospective compaction functionality test and the establishment of a compaction data bank. *Drug Dev Ind Pharm* 1993; 19: 2309–2334.
10 Parker MD, York P, Rowe RC. Binder–substrate interactions in wet granulation 3: the effect of excipient source variation. *Int J Pharm* 1992; 80: 179–190.
11 Callahan JC, Cleary GW, Elefant M, *et al.* Equilibrium moisture content of pharmaceutical excipients. *Drug Dev Ind Pharm* 1982; 8: 355–369.
12 Cooper CB, Bai TR, Heyderman E, Corrin B. Cellulose granulomas in the lungs of a cocaine sniffer. *Br Med J* 1983; 286: 2021–2022.
13 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002.* Sudbury: Health and Safety Executive, 2002.
14 Jain JK, Dixit VK, Varma KC. Preparation of microcrystalline cellulose from cereal straw and its evaluation as a tablet excipient. *Indian J Pharm Sci* 1983; 45: 83–85.
15 Singla AK, Sakhuja A, Malik A. Evaluation of microcrystalline cellulose prepared from absorbent cotton as a direct compression carrier. *Drug Dev Ind Pharm* 1988; 14: 1131–1136.
16 Doelker E, Mordier D, Iten H, Humbert-Droz P. Comparative tableting properties of sixteen microcrystalline celluloses. *Drug Dev Ind Pharm* 1987; 13: 1847–1875.
17 Bassam F, York P, Rowe RC, Roberts RJ. Effect of particle size and source on variability of Young's modulus of microcrystalline cellulose powders. *J Pharm Pharmacol* 1988; 40: 68P.
18 Dittgen M, Fricke S, Gerecke H. Microcrystalline cellulose in direct tabletting. *Manuf Chem* 1993; 64(7): 17, 19, 21.
19 Landin M, Martinez-Pacheco R, Gómez-Amoza JL, *et al.* Effect of country of origin on the properties of microcrystalline cellulose. *Int J Pharm* 1993; 91: 123–131.
20 Landin M, Martinez-Pacheco R, Gómez-Amoza JL, *et al.* Effect of batch variation and source of pulp on the properties of microcrystalline cellulose. *Int J Pharm* 1993; 91: 133–141.
21 Landin M, Martinez-Pacheco R, Gómez-Amoza JL, *et al.* Influence of microcrystalline cellulose source and batch variation on tabletting behavior and stability of prednisone formulations. *Int J Pharm* 1993; 91: 143–149.
22 Podczeck F, Révész P. Evaluation of the properties of microcrystalline and microfine cellulose powders. *Int J Pharm* 1993; 91: 183–193.
23 Rowe RC, McKillop AG, Bray D. The effect of batch and source variation on the crystallinity of microcrystalline cellulose. *Int J Pharm* 1994; 101: 169–172.
24 Hasegawa M. Direct compression: microcrystalline cellulose grade 12 versus classic grade 102. *Pharm Technol* 2002; 26(5): 50, 52, 54, 56, 58, 60.
25 Kothari SH, Kumar V, Banker GS. Comparative evaluations of powder and mechanical properties of low crystallinity celluloses, microcrystalline celluloses, and powdered celluloses. *Int J Pharm* 2002; 232: 69–80.

20 General References

Asahi Kasei Corporation. Technical literature: *Ceolus KG microcrystalline cellulose*, 2001.
Asahi Kasei Corporation. Technical literature: *Celphere microcrystalline cellulose spheres*, 2001.
DMV Pharma. Technical literature: *Pharmacel microcrystalline cellulose*, 1998.
Doelker E. Comparative compaction properties of various microcrystalline cellulose types and generic products. *Drug Dev Ind Pharm* 1993; 19: 2399–2471.
FMC Biopolymer. Technical literature: *Avicel PH microcrystalline cellulose*, 1998.
International Specialty Products. Technical literature: *Celex 101 microcrystalline cellulose*, 1997.
Penwest Pharmaceuticals Co. Technical literature: *Emcocel microcrystalline cellulose*, 1997.
Smolinske SC. *Handbook of Food, Drug, and Cosmetic Excipients.* Boca Raton, FL: CRC Press, 1992: 71–74.
Staniforth JN, Baichwal AR, Hart JP, Heng PWS. Effect of addition of water on the rheological and mechanical properties of microcrystalline celluloses. *Int J Pharm* 1988; 41: 231–236.

21 Author

PJ Weller.

22 Date of Revision

26 November 2002.

Sucrose

1 Nonproprietary Names

BP: Sucrose
JP: Sucrose
PhEur: Saccharum
USPNF: Sucrose

2 Synonyms

Beet sugar; cane sugar; α-D-glucopyranosyl-β-D-fructofuranoside; refined sugar; saccharose; sugar.

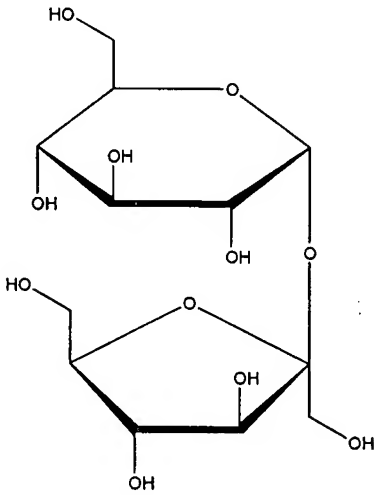
3 Chemical Name and CAS Registry Number

β-D-fructofuranosyl-α-D-glucopyranoside [57-50-1]

4 Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
$C_{12}H_{22}O_{11}$	342.30

5 Structural Formula



6 Functional Category

Base for medicated confectionery; granulating agent; sugar coating adjunct; suspending agent; sweetening agent; tablet and capsule diluent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sucrose is widely used in oral pharmaceutical formulations.

Sucrose syrup, containing 50–67% w/w sucrose, is used in tableting as a binding agent for wet granulation. In the powdered form, sucrose serves as a dry binder (2–20% w/w) or as a bulking agent and sweetener in chewable tablets and lozenges.[1] Tablets that contain large amounts of sucrose may harden to give poor disintegration.

The coprecipitation of sucrose esters with hydrophobic drugs such as nifedipine has been shown to enhance the dissolution of such drugs. Sucrose esters apparently act as a water-soluble carrier upon coprecipitation, thereby allowing hydrophobic drugs to be more readily wetted.[2]

Sucrose syrups are used as tablet-coating agents at concentrations between 50% and 67% w/w. With higher concentrations, partial inversion of sucrose occurs, which makes sugar coating difficult.

Sucrose syrups are also widely used as vehicles in oral liquid-dosage forms to enhance palatability or to increase viscosity.[3]

Because sucrose is nontoxic, biodegradable, and has good emulsifying properties, esters of sucrose have been used increasingly in cosmetic formulations.[4]

Palmitate and stearate esters of sucrose have been used to stabilize suspensions of drugs such as paracetamol. When present at concentrations up to 0.2%, these esters have successfully prevented formation of drug crystals for periods as long as 1 year.[5]

Sucrose is also widely used in foods and confectionery, and therapeutically in sugar pastes that are used to promote wound healing.[6,7] *See* Table I.

Table I: Uses of sucrose.

Use	Concentration (% w/w)
Syrup for oral liquid formulations	67
Sweetening agent	67
Tablet binder (dry granulation)	2–20
Tablet binder (wet granulation)	50–67
Tablet coating (syrup)	50–67

8 Description

Sucrose is a sugar obtained from sugar cane (*Saccharum officinarum* Linné (Fam. Gramineae)), sugar beet (*Beta vulgaris* Linné (Fam. Chenopodiaceae)), and other sources. It contains no added substances. Sucrose occurs as colorless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odorless and has a sweet taste.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Density (bulk):
  0.93 g/cm^3 (crystalline sucrose)
  0.60 g/cm^3 (powdered sucrose)
Density (tapped):
  1.03 g/cm^3 (crystalline sucrose)
  0.82 g/cm^3 (powdered sucrose)
Density (true): 1.6 g/cm^3
Dissociation constant: pK_a = 12.62
Flowability: crystalline sucrose is free flowing, whereas powdered sucrose is a cohesive solid.
Melting point: 160–186°C (with decomposition)

Table II: Pharmacopeial specifications for sucrose.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Acidity or alkalinity	+	+	—
Specific optical rotation	+66.3° to +67.0°	+66.3° to +67.0°	⩾+65.9°
Conductivity	+	+	—
Water	⩽0.1%	⩽0.1%	—
Endotoxins[a]	⩽0.25 IU/mg	⩽0.25 IU/mg	—
Dextrins[a]	+	+	—
Dextrose and invert sugar	—	+	—
Invert sugar	+	—	+
Chloride	—	—	⩽0.0035%
Sulfate	—	—	⩽0.006%
Sulfites	⩽15 ppm	⩽15 ppm	—
Calcium	—	—	+
Heavy metals	—	—	⩽5 ppm
Lead	⩽0.5 ppm	⩽0.5 ppm	—
Residue on ignition	—	—	⩽0.05%
Organic volatile impurities	—	—	+

[a] If sucrose is to be used in large volume infusions.

Moisture content: finely divided sucrose is hygroscopic and absorbs up to 1% water.[8] *See* Figure 1.

Osmolarity: a 9.25% w/v aqueous solution is isoosmotic with serum.

Particle size distribution: powdered sucrose is a white, irregular-sized granular powder. The crystalline material consists of colorless crystalline, roughly cubic granules. *See* Figure 2 and Figure 3.

Refractive index: n_D^{25} = 1.34783 (10% w/v aqueous solution)

Solubility: *see* Table III.

Table III: Solubility of sucrose.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	1 in 400
Ethanol (95%)	1 in 170
Propan-2-ol	1 in 400
Water	1 in 0.5 1 in 0.2 at 100°C

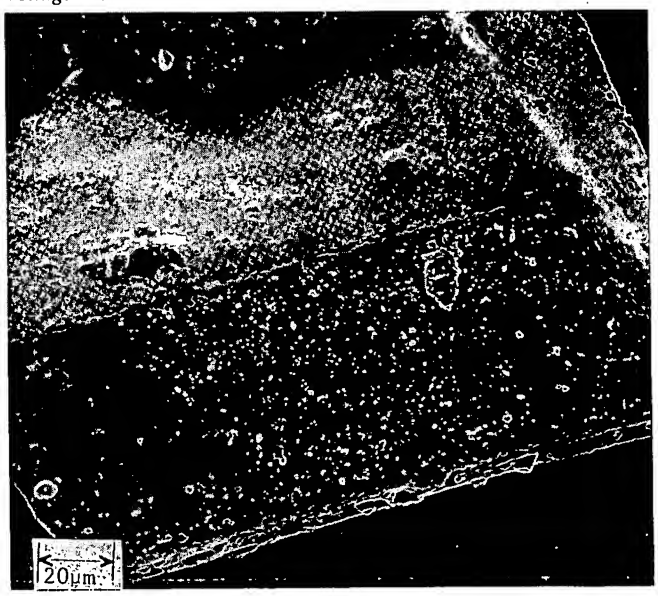
Specific gravity: *see* Table IV.

Table IV: Specific gravity of aqueous sucrose solutions.

Concentration of aqueous sucrose solution (% w/w)	Specific gravity at 20°C
2	1.0060
6	1.0219
10	1.0381
20	1.0810
30	1.1270
40	1.1764
50	1.2296
60	1.2865
70	1.3471
76	1.3854

SEM: 1
Excipient: Sucrose
Manufacturer: Great Western Sugar Co.
Lot No.: 1-2-80
Magnification: 60 ×
Voltage: 10 kV

SEM: 2
Excipient: Sucrose
Manufacturer: Great Western Sugar Co.
Lot No.: 1-2-80
Magnification: 600 ×
Voltage: 10 kV



11 Stability and Storage Conditions

Sucrose has good stability at room temperature and at moderate relative humidity. It absorbs up to 1% moisture, which is released upon heating at 90°C. Sucrose caramelizes when heated to temperatures above 160°C. Dilute sucrose solutions are liable to fermentation by microorganisms but resist decomposition at higher concentrations, e.g., above 60%

w/w concentration. Aqueous solutions may be sterilized by autoclaving or filtration.

When sucrose is used as a base for medicated confectionery, the cooking process, at temperatures rising from 110 to 145°C, causes some inversion to form dextrose and fructose (invert sugar). The fructose imparts stickiness to confectionery but prevents cloudiness due to graining. Inversion is accelerated particularly at temperatures above 130°C and by the presence of acids.

The bulk material should be stored in a well-closed container in a cool, dry place.

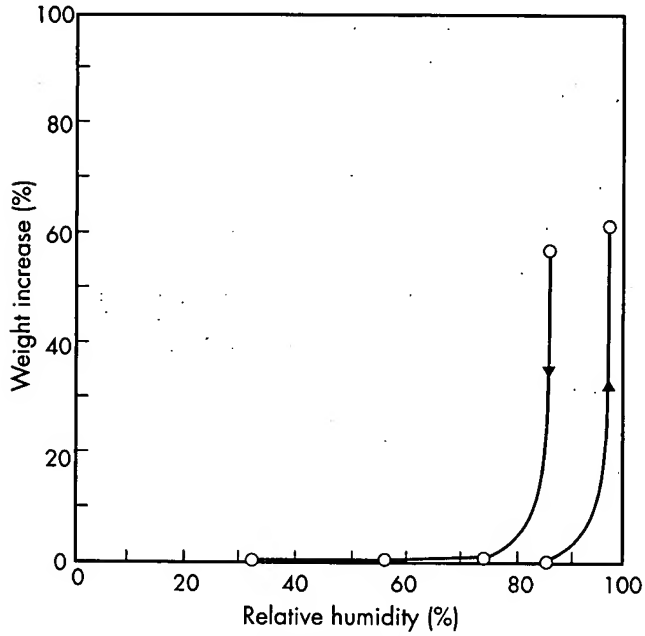


Figure 1: Moisture sorption–desorption isotherm of powdered sucrose.
Samples dried initially at 60°C over silica gel for 24 hours.
Note: at 90% relative humidity, sufficient water was absorbed to cause dissolution of the solid.

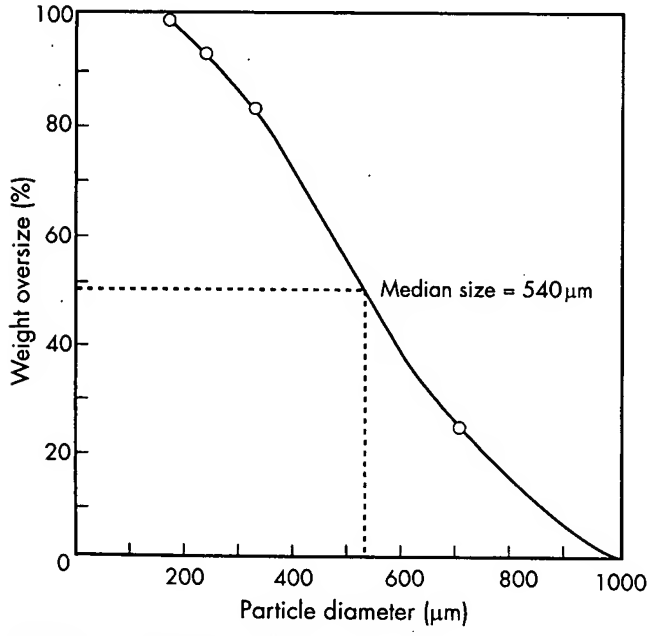


Figure 2: Particle size distribution of crystalline sucrose.

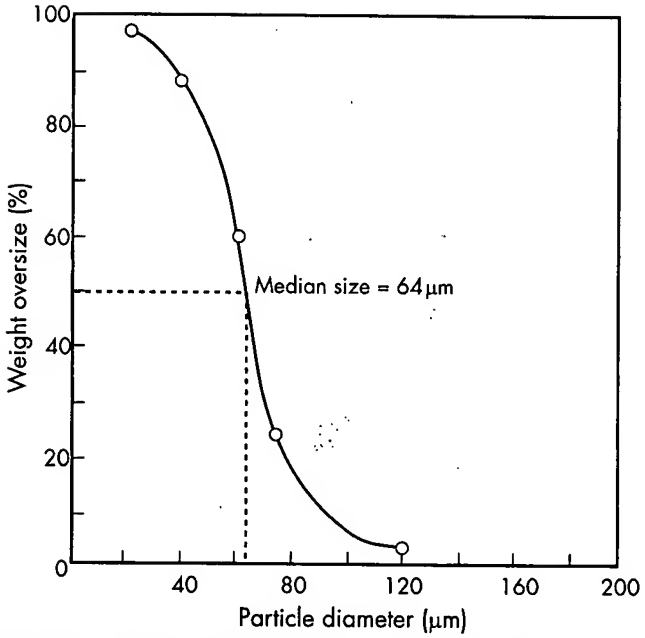


Figure 3: Particle size distribution of powdered sucrose.

12 Incompatibilities

Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients, e.g., ascorbic acid. Sucrose may also be contaminated with sulfite from the refining process. With high sulfite content, color changes can occur in sugar-coated tablets; for certain colors used in sugar-coating the maximum limit for sulfite content, calculated as sulfur, is 1 ppm. In the presence of dilute or concentrated acids, sucrose is hydrolyzed or inverted to dextrose and fructose (invert sugar). Sucrose may attack aluminum closures.[9]

13 Method of Manufacture

Sucrose is obtained from the sugar cane plant, which contains 15–20% sucrose, and sugar beet, which contains 10–17% sucrose. Juice from these sources is heated to coagulate water-soluble proteins, which are removed by skimming. The resultant solution is then decolorized with an ion-exchange resin or charcoal and concentrated. Upon cooling, sucrose crystallizes out. The remaining solution is concentrated again and yields more sucrose, brown sugar, and molasses.

14 Safety

Sucrose is hydrolyzed in the small intestine by the enzyme sucrase to yield dextrose and fructose, which are then absorbed. When administered intravenously, sucrose is excreted unchanged in the urine.

Although sucrose is very widely used in foods and pharmaceutical formulations, sucrose consumption is a cause of concern and should be monitored in patients with diabetes mellitus or other metabolic sugar intolerance.[10]

Sucrose is also considered to be more cariogenic than other carbohydrates since it is more easily converted to dental plaque. For this reason, its use in oral pharmaceutical formulations is declining.

Although sucrose has been associated with obesity, renal damage, and a number of other diseases, conclusive evidence

linking sucrose intake with some diseases could not be established.[11,12] It was, however, recommended that sucrose intake in the diet should be reduced.[12]

LD_{50} (mouse, IP): 14 g/kg[13]
LD_{50} (rat, oral): 29.7 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the occupational exposure limit for sucrose is 10 mg/m^3 long-term (8-hour TWA) and 20 mg/m^3 short-term.[14]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules, solutions, syrups, and tablets). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Compressible sugar; confectioner's sugar; invert sugar; sugar spheres.

Invert sugar
Empirical formula: $C_6H_{12}O_6$
Molecular weight: 180.16
CAS number: [8013-17-0]
Comments: an equimolecular mixture of dextrose and fructose prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar may be used as a stabilizing agent to help prevent crystallization of sucrose syrups and graining in confectionery. A 10% aqueous solution is also used in parenteral nutrition.

18 Comments

For typical boiling points of sucrose syrups, without inversion of the sugar, *see* Table V.

The EINECS number for sucrose is 200-334-9.

Table V: Boiling points of sucrose syrups.

Sucrose concentration (% w/v)	Boiling point (°C)
50	101.5
60	103
64	104
72	105.5
75	107
77.5	108.5
80	110.5

19 Specific References

1 Allen LV. Featured excipient: capsule and tablet diluents. *Int J Pharm Compound* 2000; 4(4): 306–310, 324–325.
2 Ntawukulilyayo JD, Bouckaert S, Remon JP. Enhancement of dissolution rate of nifedipine using sucrose ester coprecipitates. *Int J Pharm* 1993; 93: 209–214.
3 Salazar DSM, Saavedra C. Application of a sensorial response model to the design of an oral liquid pharmaceutical dosage form. *Drug Dev Ind Pharm* 2000; 26(1): 55–60.
4 Desai NB. Esters of sucrose and glucose as cosmetic materials. *Cosmet Toilet* 1990; 105: 99–107.
5 Ntawukulilyayo JD, DeSmedt SC, Demester J, Remon JP. Stabilization of suspensions using sucrose esters and low substituted *n*-octenylsuccinate starch–xanthan gum associations. *Int J Pharm* 1991; 128: 73–79.
6 Middleton KR, Seal D. Sugar as an aid to wound healing. *Pharm J* 1985; 235: 757–758.
7 Thomas S. *Wound Management and Dressings*. London: Pharmaceutical Press, 1990: 62–63.
8 Hancock BC, Dalton CR. Effect of temperature on water vapour sorption by some amorphous pharmaceutical sugars. *Pharm Dev Technol* 1999; 4(1): 125–131.
9 Tressler LJ. Medicine bottle caps [letter]. *Pharm J* 1985; 235: 99.
10 Golightly LK, Smolinske SS, Bennett ML, *et al*. Pharmaceutical excipients: adverse effects associated with 'inactive' ingredients in drug products (part II). *Med Toxicol* 1988; 3: 209–240.
11 Yudkin J. Sugar and disease. *Nature* 1972; 239: 197–199.
12 Anonymous. *Report on Health and Social Subjects 37*. London: HMSO, 1989.
13 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 3317.
14 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

Barry RH, Weiss M, Johnson JB, DeRitter E. Stability of phenylpropanolamine hydrochloride in liquid formulations containing sugars. *J Pharm Sci* 1982; 71: 116–118.
Czeisler JL, Perlman KP. Diluents. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, vol. 4. New York: Marcel Dekker, 1988: 37–84.
Jackson EB, ed. *Sugar Confectionery Manufacture*. Glasgow: Blackie, 1990.
Onyekweli AO, Pilpel N. Effect of temperature changes on the densification and compression of griseofulvin and sucrose powders. *J Pharm Pharmacol* 1981; 33: 377–381.
Wolraich ML, Lindgreen SD, Stumbo PJ, *et al*. Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *N Engl J Med* 1994; 330: 301–307.

21 Author

NA Armstrong.

22 Date of Revision

17 October 2002.

Sugar, Compressible

1 Nonproprietary Names

USPNF: Compressible sugar

2 Synonyms

Di-Pac; direct compacting sucrose.

3 Chemical name and CAS Registry Number

See Section 4 and Section 18.

4 Empirical Formula Molecular Weight

The USPNF 20 states that compressible sugar contains not less than 95.0% and not more than 98.0% of sucrose ($C_{12}H_{22}O_{11}$). It may contain starch, maltodextrin, or invert sugar, and may contain a suitable lubricant.

5 Structural Formula

See Section 4.

6 Functional Category

Sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Compressible sugar is used primarily in the preparation of direct-compression chewable tablets. Its tableting properties can be influenced by small changes in moisture level;[1,2] *see* Table I.

Table I: Uses of compressible sugar.

Use	Concentration (%)
Dry binder in tablet formulations	5–20
Filler in chewable tablets	20–60
Filler in tablets	20–60
Sweetener in chewable tablets	10–50

8 Description

Compressible sugar is a sweet-tasting, white, crystalline powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for compressible sugar.

Test	USPNF 20
Identification	+
Calcium	+
Chloride	≤0.014%
Heavy metals	≤5 ppm
Loss on drying	0.25–1.0%
Residue on ignition	≤0.1%
Microbial limits	+
Organic volatile impurities	+
Sulfate	≤0.010%
Assay	95.0–98.0%

10 Typical Properties

Density (bulk): 0.492 g/cm^3
Density (tapped): 0.6 g/cm^3
Moisture content: 0.57%
Particle size distribution: for *Di-Pac*, 3% maximum retained on a #40 (425 µm) mesh; 75% minimum through a #100 (150 µm) mesh; 5% maximum through #200 (75 µm) mesh.
Solubility: the sucrose portion is water-soluble.
Specific surface area: 0.13–0.14 m^2/g

11 Stability and Storage Conditions

Compressible sugar is stable in air under normal storage conditions of room temperature and low relative humidity. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with dilute acids, which cause hydrolysis of sucrose to invert sugar, and with alkaline earth hydroxides, which react with sucrose to form sucrates.

13 Method of Manufacture

Compressible sugar is prepared by cocrystallization of sucrose with other excipients such as maltodextrin.[1] Compressible sugar may also be prepared using a dry granulation process.

14 Safety

Compressible sugar is generally regarded as a relatively nontoxic and nonirritant material. *See also* Sucrose.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. *See also* Sucrose.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Confectioner's sugar; sucrose; sugar spheres; Sugartab.

Sugartab

Appearance: *Sugartab* (Penwest Pharmaceuticals Co.) is a compressible sugar that does not conform to the USPNF 20 specification. It is an agglomerated sugar product containing approximately 90–93% sucrose, the balance being invert sugar.
Density (bulk): 0.60 g/cm^3
Density (tapped): 0.69 g/cm^3
EINECS number: [64333-34-2]
Flowability: 42.7 g/s
Moisture content: 0.20–0.57%.
Particle size distribution: 30% through a #20 (850 μm) mesh; 3% through a #30 (600 μm) mesh.

18 Comments

—

19 Specific References

1 Rizzuto AB, Chen AC, Veiga MF. Modification of the sucrose crystal structure to enhance pharmaceutical properties of excipient and drug substances. *Pharm Technol* 1984; 8(9): 32, 34, 36, 38–39.
2 Tabibi SE, Hollenbeck RG. Interaction of water vapor and compressible sugar. *Int J Pharm* 1984; 18: 169–183.

20 General References

Mendes RW, Gupta MR, Katz IA, O'Neil JA. Nu-tab as a chewable direct compression carrier. *Drug Cosmet Ind* 1974; 115(6): 42–46,130–133.
Ondari CO, Kean CE, Rhodes CT. Comparative evaluation of several direct compression sugars. *Drug Dev Ind Pharm* 1983; 9: 1555–1572.
Ondari CO, Kean CE, Rhodes CT. Comparative evaluation of several direct compression sugars. *Drug Dev Ind Pharm* 1988; 14: 1517–1527.
Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression. *Pharm Technol* 1981; 5: 69–78.

21 Author

AW Wood.

22 Date of Revision

8 October 2002.

Sugar, Confectioner's

1 Nonproprietary Names

USPNF: Confectioner's sugar

2 Synonyms

Icing sugar; powdered sugar.

3 Chemical Name and CAS Registry Number

See Section 4.

4 Empirical Formula Molecular Weight

The USPNF 20 describes confectioner's sugar as a mixture of sucrose ($C_{12}H_{22}O_{11}$) and corn starch that has been ground to a fine powder; it contains not less than 95.0% sucrose.

5 Structural Formula

See Section 4 and Sucrose.

6 Functional Category

Sugar coating adjunct; sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Confectioner's sugar is used in pharmaceutical formulations when a rapidly dissolving form of sugar is required for flavoring or sweetening. It is used as a diluent in solid-dosage formulations when a small particle size is necessary to achieve content uniformity in blends with finely divided active ingredients. In solutions, at high concentrations (70% w/v), confectioner's sugar provides increased viscosity along with some preservative effects. Confectioner's sugar is also used in the preparation of sugar-coating solutions and in wet granulations as a binder/diluent. *See* Table I.

Table I: Uses of confectioner's sugar.

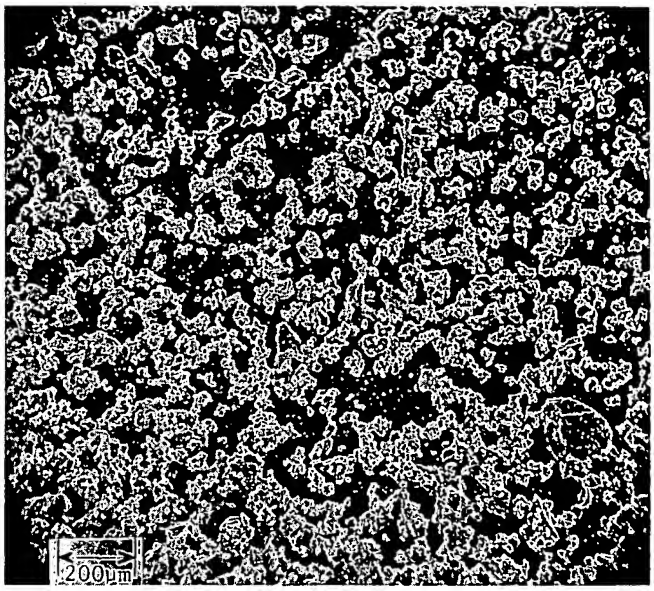
Use	Concentration (%)
Sweetening agent in tablets	10–20
Tablet diluent	10–50

See also Section 18.

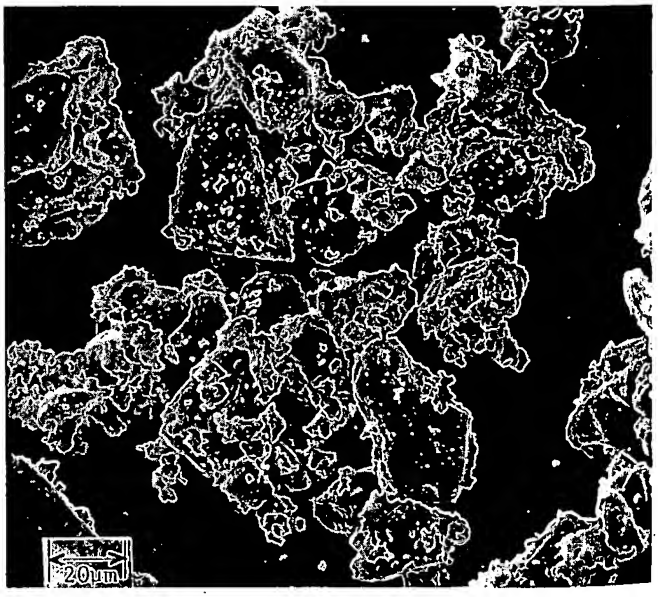
8 Description

Confectioner's sugar occurs as a sweet-tasting, fine, white, odorless powder.

SEM: 1
Excipient: Confectioner's sugar
Manufacturer: Frost
Lot No.: 101A-1
Magnification: 60 ×
Voltage: 20 kV



SEM: 2
Excipient: Confectioner's sugar
Manufacturer: Frost
Lot No.: 101A-1
Magnification: 600 ×
Voltage: 20 kV



9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for confectioner's sugar.

Test	USPNF 20
Identification	+
Chloride	≤0.014%
Calcium	+
Heavy metals	≤5 ppm
Loss on drying	≤1.0%
Microbial limits	+
Organic volatile impurities	+
Residue on ignition	≤0.08%
Specific rotation	≥62.6°
Sulfate	≤0.006%
Assay	≤95.0%

10 Typical Properties

Density (bulk): 0.465 g/cm^3
Density (tapped): 0.824 g/cm^3
Moisture content: 0.1–0.31%
Particle size distribution: various grades with different particle sizes are commercially available, e.g., 6X, 10X, and 12X grades of confectioner's sugar from the Domino Sugar Corp. Mean particle size is 14.3 μm.
For 6X, 94% through a #200 (75 μm) mesh
For 10X, 99.9% through a #100 (150 μm) mesh and 97.5% through a #200 (75 μm) mesh
For 12X, 99% through a #200 (75 μm) mesh and 96% through a #325 (45 μm) mesh.
Solubility: the sucrose portion is water-soluble while the starch portion is insoluble in water, although it forms a cloudy solution.

11 Stability and Storage Conditions

Confectioner's sugar is stable in air at moderate temperatures but may caramelize and decompose above 160°C. It is more hygroscopic than granular sucrose. Microbial growth may occur on dry storage if adsorbed moisture is present or in dilute aqueous solutions.

Confectioner's sugar should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Confectioner's sugar is incompatible with dilute acids, which cause the hydrolysis of sucrose to invert sugar. It is also incompatible with alkaline earth hydroxides, which react with sucrose to form sucrates.

13 Method of Manufacture

Confectioner's sugar is usually manufactured by grinding refined granulated sucrose with corn starch to produce a fine powder. Other anticaking agents, such as tricalcium phosphate and various silicates, have also been used but are less common.

14 Safety

Confectioner's sugar is used in confectionery and oral pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material. *See also* Sucrose.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. *See also* Sucrose.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (capsules and tablets).

17 Related Substances

Compressible sugar; sucrose; sugar spheres.

18 Comments

Confectioner's sugar is not widely used in pharmaceutical formulations because the poor-flow characteristics prevent its use in direct-compression blends. However, confectioner's sugar is used when a smooth mouth feel or a rapidly dissolving sweetener is required, and when a milled/micronized active ingredient must be blended with a diluent of similar particle size for powders or wet granulations.

Low-starch grades of confectioner's sugar containing 0.01% w/w starch are also commercially available.

19 Specific References

—

20 General References

Barry RH, Weiss M, Johnson JB, DeRitter E. Stability of phenylpropanolamine hydrochloride in liquid formulations containing sugars. *J Pharm Sci* 1982; 71: 116–118.

Czeisler JL, Perlman KP. Diluents. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, vol. 4. New York: Marcel Dekker, 1988: 37–84.

Edwards WP. *The Science of Sugar Confectionery*. Cambridge: Royal Society of Chemistry, 2000.

Jackson EB, ed. *Sugar Confectionery Manufacture*. Glasgow: Blackie, 1990.

Onyekweli AO, Pilpel N. Effect of temperature changes on the densification and compression of griseofulvin and sucrose powders. *J Pharm Pharmacol* 1981; 33: 377–381.

Wolraich ML, Lindgren SD, Stumbo PJ, *et al.* Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *N Engl J Med* 1994; 330: 301–307.

21 Author

AH Kibbe.

22 Date of Revision

8 October 2002.

Sugar Spheres

1 Nonproprietary Names

BP: Sugar spheres
PhEur: Sacchari spheri
USPNF: Sugar spheres

2 Synonyms

Non-pareil; non-pareil seeds; *NPTAB*; *Nu-Core*; *Nu-Pareil PG*; sugar seeds; *Suglets*.

3 Chemical Name and CAS Registry Number

—

4 Empirical Formula Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations.[1–4] They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.

Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating.

Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8 Description

The USPNF 20 describes sugar spheres as approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch.

The PhEur 2002 states that sugar spheres contain not more than 92% of sucrose calculated on the dried basis. The remainder consists of corn (maize) starch and may also contain starch hydrolysates and color additives. The diameter of sugar spheres varies from 200 to 2000 µm and the upper and lower limits of the size of the sugar spheres are stated on the label.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sugar spheres.

Test	PhEur 2002	USPNF 20
Identification	+	+
Heavy metals	≤5 ppm	≤5 ppm
Loss on drying	≤5.0%	≤4.0%
Microbial limits	+	+
Organic volatile impurities	—	+
Particle size distribution	+	+
Residue on ignition	≤0.2%	≤0.25%
Specific rotation	—	+41° to +61°
Sucrose (dried basis)	≤92%	62.5–91.5%

10 Typical properties

Density:
1.57–1.59 g/cm^3 for *Suglets* less than 500 µm in size
1.55–1.58 g/cm^3 for *Suglets* more than 500 µm in size

Flowability: <10 seconds; free flowing.

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available from various suppliers (US standard sieves):

45–60 mesh (250–355 µm)
40–50 mesh (300–425 µm)
35–45 mesh (355–500 µm)
35–40 mesh (420–500 µm)
30–35 mesh (500–600 µm)
25–30 mesh (610–710 µm)
20–25 mesh (710–850 µm)
18–20 mesh (850–1000 µm)
16–20 mesh (850–1180 µm)
14–18 mesh (1000–1400 µm)

Solubility: solubility in water varies according to the sucrose-to-starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.

Specific surface area:
0.1–0.2 m^2/g for *Suglets* less than 500 µm in size
>0.2 m^2/g for *Suglets* more than 500 µm in size

11 Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Starch and Sucrose for information concerning the incompatibilities of the component materials of sugar spheres.

13 Method of Manufacture

Sugar spheres are prepared from crystalline sucrose, which is coated using sugar syrup and a starch dusting powder.

14 Safety

Sugar spheres are used in oral pharmaceutical formulations. The sucrose and starch components of sugar spheres are widely used in edible food products and oral pharmaceutical formulations.

The adverse reactions and precautions necessary with the starch and sucrose components should be considered in any product containing sugar spheres. For example, sucrose is generally regarded as more cariogenic than other carbohydrates, and in higher doses is also contraindicated in diabetic patients.

See Starch and Sucrose for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK and Europe. The sucrose and starch components of sugar spheres are individually approved for use as food additives in Europe and the USA.

17 Related Substances

Compressible sugar; confectioner's sugar; starch; sucrose.

18 Comments

—

19 Specific References

1 Narsimhan R, Labhasetwar VD, Lakhotia CL, Dorle A. Timed-release noscapine microcapsules. *Indian J Pharm Sci* 1988; 50: 120–122.
2 Bansal AK, Kakkar AP. Solvent deposition of diazepam over sucrose pellets. *Indian J Pharm Sci* 1990; 52: 186–187.
3 Ho H-O, Su H-L, Tsai T, Sheu M-T. The preparation and characterization of solid dispersions on pellets using a fluidized-bed system. *Int J Pharm* 1996; 139: 223–229.
4 Miller RA, Leung EM, Oates RJ. The compression of spheres coated with an aqueous ethylcellulose dispersion. *Drug Devel Ind Pharm* 1999; 25(4): 503–511.

20 General References

Birch GG, Parker KJ, eds. *Sugar: Science and Technology*. London: Applied Science Publications, 1979.

21 Author

RC Moreton.

22 Date of Revision

7 October 2002.